REMARKS/ARGUMENTS

Claim Rejections - 35 U.S.C. § 112 - First Paragraph

The rejection of claims 29 and 30 under this section is respectfully traversed. The full scope of the claimed invention in these claims is a dosage form in the form of a layered tablet, and the specification expressly teaches how to make and administer the dosage form. No undue experimentation is necessary since all steps for making and using are fully described in the specification, particularly when considered in the context of the state of the art, where layered dosage forms of various kinds exist and their manufacture and administration are well known. There is no lack of predictability in combining the listed ingredients, tabletting them in layers, and administering them to a subject, and this is all that is needed to satisfy 35 U.S.C. § 112, first paragraph. Whatever the teachings of Richardson et al. US 6,207,190, Jones et al. US 6,013,632, and Fahim US 4,937,234 are, these references do not lessen the quality of the information presented in the instant specification, much less indicate in any way that the components listed in Applicants' claims *cannot* be made into a layered tablet dosage form or administered orally to a patient.

Claim Rejections - 35 U.S.C. § 103(a)

The rejection of claims 29 and 30 as unpatentable for obviousness over Jones et al. US 6,013,632 and Murad US 5,804,594 in view of Richardson et al. US 6,207,190 is respectfully traversed.

The dosage form expressed in these claims is indeed unique and has unique benefits in clinical applications. It permits patients who are physiologically unable to absorb clinically appropriate amounts of some active ingredients to do so when those elements are delivered in serial bolus amounts. Diabetics and the elderly, for example, have irregular and frequently inadequate absorption rates, and even healthy, normal patients have an upper limit of 8 mEq for the absorption of magnesium when delivered as a single bolus. By delivering such a rate-limited ingredient in segmented amounts, absorption is not only more efficient, but in some

cases, it may be the only means by which appropriate amounts of the ingredient can be adequately delivered without unpredictable side effects.

It is known that the absorption of ingredients is greatly modified by the intestinal environment. The examiner's attention is directed to two of the three reference documents supplied herewith as part of Applicants' Information Disclosure Statement -- Hardwick, L. L., et al. "Site and mechanism of intestinal magnesium absorption," *Miner. Electrolyte Metab.* **16** (2-3): 174-80 (1990); and Fine, K. D., et al. "Intestinal absorption of magnesium from food and supplements," *J. Clin. Invest.* **88** (2): 396-02 (1991). The absorptivity of these ingredients is especially dependent on pH which differs in different portions of the intestinal tract. The bi-layered dosage form of the present invention takes this environmental physiology into consideration and provides a better-designed clinical alternative. Magnesium oxide, for example, is included in the gastric, immediate-release section of the bi-layered tablet because magnesium oxide requires an acid environment to be converted into magnesium chloride, which is more useful and absorbable; magnesium ascorbate and/or magnesium taurate, on the other hand, are more effectively absorbed in the alkaline environment of the distal intestine and are accordingly placed in the sustained-release section of the tablet. This distribution of different molecules between different parts of the intestine permits greater amounts of magnesium to be delivered without exceeding the maximum absorption capabilities of the gut and permits distribution of an active ingredient between two different chemical environments to take advantage of the different efficiencies of each compartment. This is only one example of how the bi-layered structure of the present invention capitalizes upon the differences in physiology represented by different regions of the intestine. Other examples are the regional variability in transport sites per enterocyte, changes in the affinity of transporters for various substrates, and solute depletion at the various membranes involved. The present invention targets the appropriate ingredient deliveries by virtue of its variable-release dosage form of delivery.

Certain active ingredients, such as magnesium, zinc, and copper, compete for a limited intestinal capacity to absorb metals. It they are delivered simultaneously to the same region of the intestine, absorption rates for each are difficult to determine and quite hard to predict – this is an area of gastrointestinal physiology that is not well understood. Sequencing

the delivery of these elements to different parts of the intestine, in the presence of differing intestinal environments, decreases the competition for absorption and raises the likelihood that desired amounts of each metal will enter the metabolic stream.

In some cases, sequential release is the only way that appropriate amounts of some active ingredients can be delivered to a given patient. A single-release tablet may be almost totally ineffective in controlling the delivery, or effecting appropriate delivery of desired ingredients, for some patients. The unique dosage form of the present invention with its sequenced delivery provides a solution to this problem.

As mentioned in the specification, magnesium and ascorbate operate synergistically against the herpes virus. The dosage form of the present invention patent delivers magnesium oxide, magnesium ascorbate (or magnesium taurate) and lysine ascorbate in segregated amounts to avoid competition between the absorption of magnesium and the other metals of the formulation (copper and zinc), in order to better control the availability of both magnesium (in any of its forms) and ascorbate (in either of its forms). The same is true for the sequential delivery of quercetin, whose absorption patterns are not well understood. It is known, however, that the presence of ascorbic acid inhibits the absorption of quercetin. The bilayer dosage form of the present invention provides better confidence that adequate amounts of quercetin will be present to act synergistically with either acyclovir or 5-ethyl-2'-deoxyuridine if these very commonly used antiviral agents are prescribed.

None of these effects are disclosed or suggested in any of the three cited references, either alone or in combination, and reconsideration of this rejection is therefore respectfully requested.

Claim Rejections - 112 - First Paragraph

The expression "conditions giving rise thereto" is deleted from the claims by the above amendment.

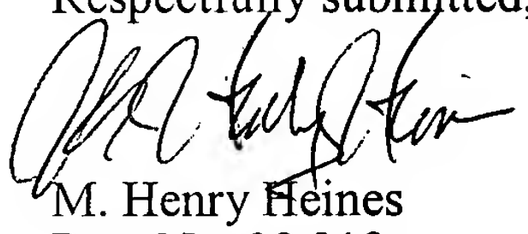
Nonstatutory Obviousness-Type Double-Patenting

This rejection is obviated by the enclosed Terminal Disclaimer.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance, and reconsideration of the application is therefore respectfully requested. Should any matters remain that can be resolved by a conference with Applicants' attorney, the examiner is encouraged to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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